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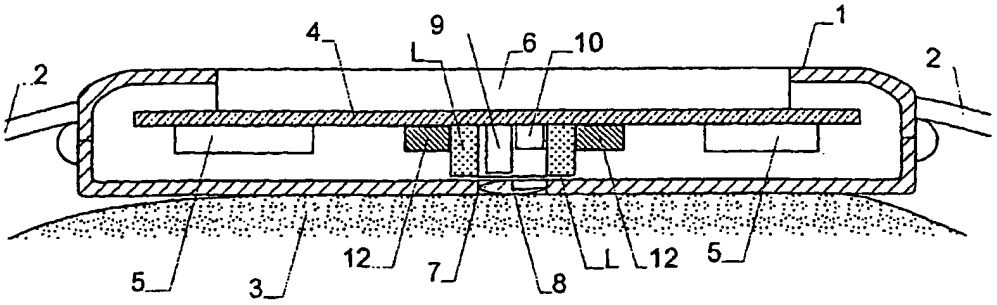
(54) Title: METHOD AND DEVICE FOR BLOOD COMPONENT CONCENTRATION DETERMINATION



(57) Abstract: For the non-invasive determination of a concentration of a component in blood, in particular for the determination of the concentration of blood sugar, an electric coil (L) arranged at the body is periodically operated with current pulses. After the current pulses, the voltage (U_L) over the voltage is determined. It is found that the temporal evolution of this voltage (U_L) depends on the concentration of the components to be measured if the frequency of the current pulse corresponds to an experimentally determined resonance frequency. The measuring method can e.g. be carried out by a device designed as wrist watch.

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METHOD AND DEVICE FOR BLOOD COMPONENT CONCENTRATION DETERMINATION

Cross References to Related Applications

This application claims the priority of European patent application 99810933.4, filed October 13, 1999, the disclosure of which is incorporated herein by reference in its entirety.

Technical Field

The invention relates to a method for the non-invasive determination of the concentration of at least one component in blood and to a device for carrying out this method according to the preamble of the independent claims. Such methods or devices, respectively, are in particular used for determining the glucose concentration in blood.

Background Art

For measuring the concentration of glucose in blood, invasive blood collection is usually required. Since such blood collection is undesired for obvious reasons, alternative non-invasive procedures are searched for. It has e.g. been tried to determine glucose in blood by means of laser light, which, however, does not yield satisfactory results because the results strongly depend on temperature, physical exercise, sun tan, etc. This is a consequence of the fact that a measurement by means of laser light can only sample a comparatively small subcutaneous region of the tissue with a depth a approximately 3 mm.

Further devices and methods are known where the glucose in blood is measured by means of nuclear resonance. This requires, however, the generation of very strong permanent magnetic fields, which makes corresponding apparatus heavy and expensive.

WO 95/04496 describes a method based on an impedance measurement of the human body. It involves the application of electrodes to the body, which makes the measurement dependent on skin humidity and pressure applied to the electrodes. Furthermore, it requires complex electronics for processing the measured signal.

Disclosure of the Invention

Therefore, the problem to be solved lies in providing a method and apparatus of the type mentioned initially that yield accurate results in simple manner without requiring invasive blood collection.

This problem is solved by the independent claims.

In a preferred embodiment of the method a coil is brought within range of the body surface. Then, a measuring value depending on the inductance or loss of the coil, preferably the inductance, is measured at least at one frequency, and from this value the desired concentration of the component is e.g. determined by means of a suited calibration function.

In a further aspect of the invention, a device comprising a coil, a holder for attaching the coil and a driver for generating a periodically changing current in the coil is provided. A detector is used for detecting at least one measured signal depending on the temporal evolution of a voltage over or a current through the coil. It is found that the desired concentration can be derived from such a measured signal using suited calibration data.

In contrast to measuring devices based on the determination of nuclear resonant oscillations, no permanent magnetic field source is required of a size and direction where nuclear resonant oscillations could occur at the excitation frequencies.

Brief Description of the Drawings

The invention will be better understood and objects other than those set forth above will become apparent when consideration is given to the following detailed description thereof. Such description makes reference to the annexed drawings, wherein:

Fig. 1 is a sectional view of an embodiment of the device according to the invention,

Fig. 2 is a circuit block diagram of the device of Fig. 1,

Fig. 3 is the driver for the measuring coil,

Fig. 4 is the temporal evolution of the currents in Fig. 3,

Fig. 5 is a comparative table of measured and reference results.

Modes for Carrying Out the Invention

A preferred mechanical set-up of the device in the shape of a wristwatch is shown in Fig. 1. It comprises a housing 1, which is held to a body surface 3 by means of a holder or wristband 2. A support 4 is arranged in the housing 1, which support carries an electronic circuit 5 and a liquid crystal display 6. An opening 7 is provided on the side of the housing 1 that faces the body. Optics 8 are arranged in the opening 7. A light

source 9 and a light sensor 10 are arranged behind the optics, wherein the light sensor 10 is positioned such that it receives light of the light source 9 reflected from the body. A cylindrical electrical coil L is arranged around the light source 9 and the light sensor 10, the axis of the coil being perpendicular to the body surface. A further small permanent magnet 12 can be arranged in or beside coil L, the field of which permanent magnet is substantially parallel to the one of the coil. Even though such a permanent magnet is not absolutely required, it is found that its field improves the quality of the measured signals.

Fig. 2 shows a block diagram of the circuit of the device of Fig. 1. It comprises a microprocessor 14 connected to an input and output section 15. The latter comprises the display 6 as well as conventional control elements that can be operated by the user. The microprocessor 14 and the input and output section 15 possess all capabilities of a conventional wristwatch. Beyond that, the microprocessor is, however, capable to measure the glucose level or other components in the body tissue. For this purpose, it is connected via a driver circuit 16 to coil L. Furthermore, a driver stage 17 is provided for driving the light source 9, which consists of three LEDs 9a, 9b, 9c of differing color (preferably red, yellow, and green or blue). The signals of the light sensor 10 are fed to an amplifier 18 with A/D-converter and then also to microprocessor 14.

The driver circuit 16 for coil L is shown in Fig. 3. It comprises two complementary transistors T1, T2, which are individually controlled by microprocessor 14 by means of signals U1, U2. The output of the complementary transistor pair T1, T2, which are arranged between a supply voltage and ground, is connected to one terminal of coil L. The second terminal of coil L is on ground. A threshold value detector 20 measures the voltage U_L over the coil and generates a signal as soon as

the absolute value of the voltage U_L is above a threshold value U_T.

The operation of the driver circuit 16 is illustrated in Fig. 4. Microprocessor 15 first switches on the upper transistor T1 during a first measuring phase, which causes the voltage U_L over the coil to rise to the value of the positive supply voltage. Then, transistor T1 is switched off while transistor T2 remains switched off during a second measuring phase. During this second measuring phase, the driver circuit 16 is therefore in high impedance state. Disconnecting the coil from the voltage U_L generates a negative induction voltage over the coil. At the same time, the output "Out" of the threshold value detector 20 goes from 0 to 1. When the value of the voltage U_L drops, after a time T_X, below the threshold value U_T, the output "Out" goes from 1 to 0. Then, after a predefined time, at the end of the second measuring phase, the lower transistor T2 can optionally be switched on for fully discharging the voltage over the coil. Thereafter, the measuring cycle starts anew with the first measuring phase.

The output "Out" is fed to microprocessor 15, which determines the time T_X. This determination can e.g. be carried out by a suitable fast counter or analogue integration of the signal and analog-digital conversion thereof.

The time T_X depends on the inductance and loss (or quality factor Q) of the coil L, which, among other things, also depends on the magnetic and conductive properties of the tissue and blood of the user. In particular, it has been found that the coil inductance and/or loss and the value of T_X are a function of the blood composition. Depending on the length of the measuring period T_p or the excitation frequency $F = 1/T_p$, different components can be measured selectively. For example, the preferred frequency F for determining the blood sugar level is approximately 75.80 MHz, i.e. at this fre-

quency the value of the coil inductance and loss or the time T_X depends strongly on the blood sugar level.

For other components, other measurement frequencies can be used, such as 75.95 MHz for the determination of the concentration of NaCl in solution or 86.4 MHz for insulin. The measurement frequency for a component is determined by calibration measurements, wherein probes of differing concentration of the component are measured. For each probe, the inductance and/or loss or the value of T_X is measured as a function of the frequency F. The spectra measured in this way are compared to each other, and the frequency showing the strongest dependence of the measured signal from the component's concentration is used as measurement frequency. A preferred range of frequencies F lies between 10 kHz and 1 GHz, preferably between 10 MHz and 1 GHz, in particular between 50 MHz and 200 MHz. It is, however, also possible to measure at other frequencies.

In the present embodiment the device only determines the blood sugar level and is fixedly set to the frequency 75.87 MHz. It is, however, also possible to vary the measuring frequency for measuring the concentration of other components.

The value of the measuring signal not only depends on the concentration of the component to be measured, but also on the quantity of blood in the measuring range. Since the quantity of blood can vary e.g. depending on blood circulation in the vessels or because of variations in blood pressure, it is preferred to run a second measurement. This second measurement can e.g. be based on the method described above and determine the concentration of a second blood component in the measuring area, whereby the amount of blood can be determined and the blood sugar value can be corrected.

A further improvement can be achieved by an additional optical measurement. For this purpose, the magnitude of the signal received by light sensor 10, i.e.

the reflected light, is determined. This signal, i.e. the reflection coefficient of the body, also depends of the amount of blood in the analyzed tissue.

It is found that the signal of light sensor 10, after suited scaling, can simply be added to the value T_X for producing more reliable results.

Preferably, the measuring signal T_X, possibly after an addition to the signal from the light sensor, is converted into the desired blood sugar level by means of a calibration table or calibration coefficient. For this purpose, a calibration step is performed where the measured signal is compared to a blood sugar level that was determined in conventional manner. The number of calibration measurements depends on the desired accuracy. For most applications, one calibration measurement above 10 mmol/lt and one between 4 and 6 mmol/lt is sufficient.

The calibration step allows to calculate a calibration function (consisting e.g. of a calibration factor or a calibration table). Preferably, this calibration step is repeated for each new user.

In the embodiment shown here, light with a very broad spectrum is generated by means of three light emitting diodes of differing colors. It is also possible to use other light sources.

Fig. 5 shows a table of measurements of a calibrated device in comparison with analytically found reference results. It is found that the present method has a high accuracy.

The inventor assumes that in the present method the magnetic pulses of coil L excite intermolecular oscillations in the blood, and in particular also in frequency ranges below 1 GHz. The inductance and/or loss of the coil L and the value of the time T_X depend on the amplitude of the excited oscillations.

A possible measurement range is between 10 kHz and 1 GHz, a preferred measurement range is 10 MHz to

1 GHz, wherein it a range between 50 MHz and 200 MHz has been found to be especially suited for measurements.

In the present embodiment, a periodic electromagnetic signal is applied and a coupling of the electromagnetic field and the atoms and/or bonds of the molecule is used. It is, however, also suggested to use in addition to the coil L, a piezoelectric emitter 22 for sound or ultrasound, which generates mechanical oscillations and receives corresponding echoes.

While there are shown and described presently preferred embodiments of the invention, it is to be distinctly understood that the invention is not limited thereto but may be otherwise variously embodied and practiced within the scope of the following claims.

Claims

1. A method for the non-invasive determination of the concentration of a substance in blood, in particular for the determination of the concentration of glucose in blood, comprising the steps of

measuring a measuring signal depending on one of the inductance or the loss of a coil (L) located in the vicinity of a surface of a body while an alternating electromagnetic field generated by said coil extends into said body and

using calibration data for converting said measuring signal to said concentration.

2. The method of claim 1 comprising the step of measuring a signal depending on the inductance the coil (L).

3. A method for the non-invasive determination of the concentration of a substance in blood, in particular for the determination of the concentration of glucose in blood, comprising the steps of

sending periodic current pulses having a given repetition rate through a coil (L) located in the vicinity of a surface of a body and generating an electromagnetic field in said body, said electromagnetic field having no magnetic components sufficient for generating NMR oscillations at the given repetition rate,

determining, between said current pulses, a measured signal, said measured signal depending on the temporal evolution of at least one of the current through the coil or a voltage over the coil,

using calibration data for converting said measured signal to said concentration.

4. The method of claim 3 wherein said measured signal (T_X) corresponds to a time required by said current to fall below a given threshold.

5. A device for the non-invasive determination of the concentration of a substance in blood, in

particular for the determination of the concentration of glucose in blood, comprising

an electric coil (L),

a holder (2) for attaching the coil close to the surface of a body,

a driver (T1, T2) generating a periodically changing current in the coil at a given repetition rate (F), and

a detector (20) detecting at least one measured signal (T_X) from the temporal evolution of at least one of the current through the coil or a voltage over the coil and deriving the concentration from the measured signal,

said device not comprising a source for a permanent magnetic field of a magnitude and direction suited for causing NMR oscillations under the operation of said coil.

6. The device of claim 5 further comprising a light source (9) generating light for irradiating said surface and a light detector (10) for measuring reflected light and means for additive combination of a reflection coefficient measured by the light detector and the measured signal.

7. The device of claim 6 wherein the coil is arranged around the light source (9) and the light detector (10).

8. The device of one of the claims 5 - 7 further comprising a wrist watch housing (1), a time display (15) and a wristband.

9. The device of one of the claims 5 - 8 wherein said repetition rate is between 10 kHz and 1 GHz.

10. The device of one of the claims 5 - 9 wherein said repetition rate is between 10 MHz and 1 GHz.

11. The device of one of the claims 5 - 10 wherein said repetition rate is between 50 MHz and 200 MHz.

12. The device of one of the claims 5 - 11 wherein said repetition rate is 75.8 MHz for the detection of glucose.

13. The device of one of the claims 5 - 12 wherein said driver (T1, T2) is adapted to generate periodic, repetitive current pulses in the coil (L).

14. The device of claim 13 wherein said driver (T1, T2) is adapted to apply a voltage over said coil during a first measuring phase for generating one of said current pulses and to go to a high impedance state during a second measuring phase during measuring of the time evolution.

15. The device of one of the claims 5 - 14 wherein said measured signal (T_X) corresponds to a decay time of said current.

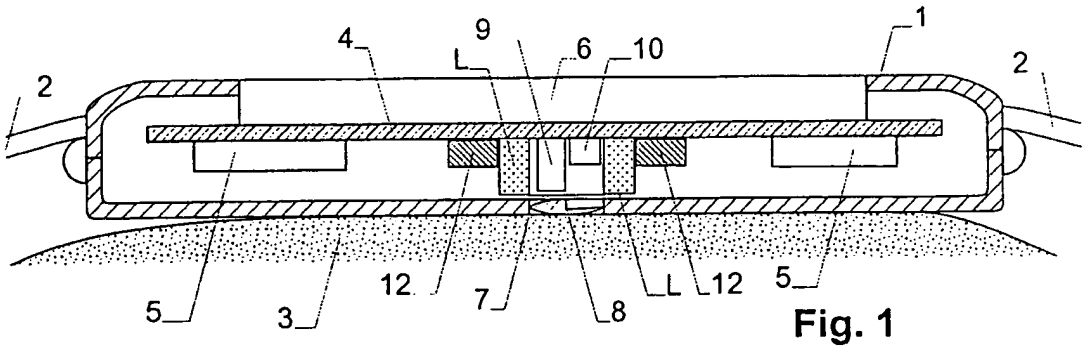

Fig. 1

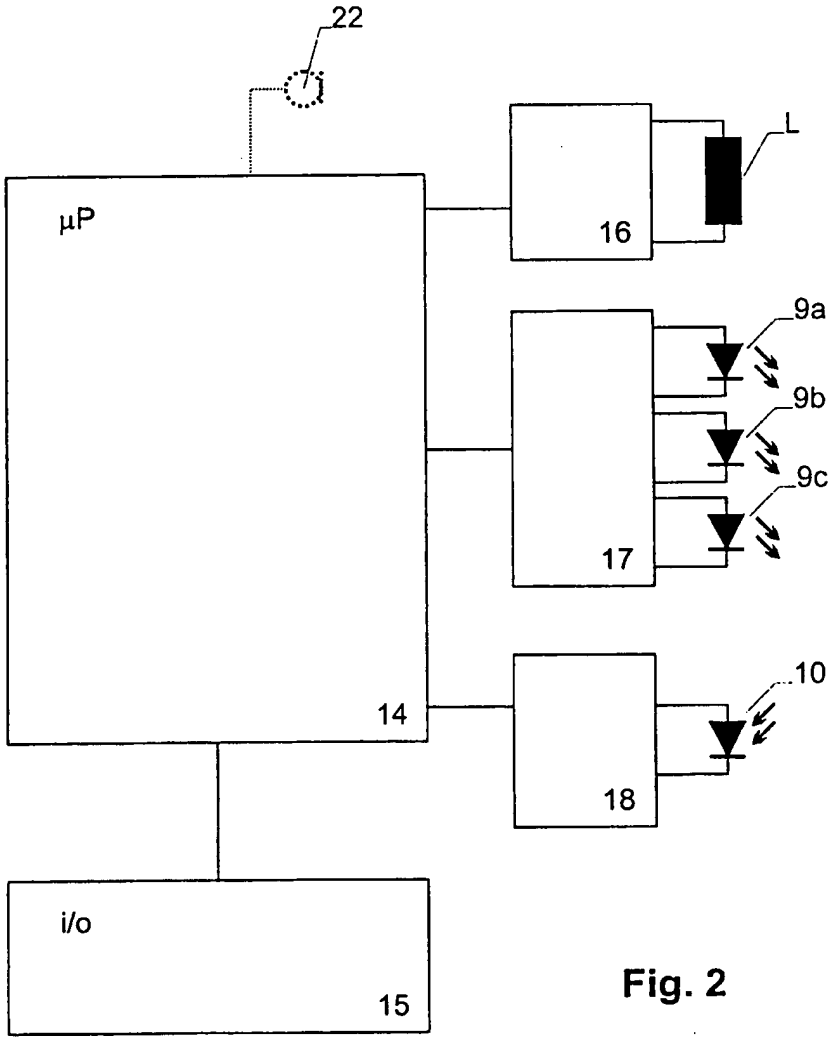

Fig. 2

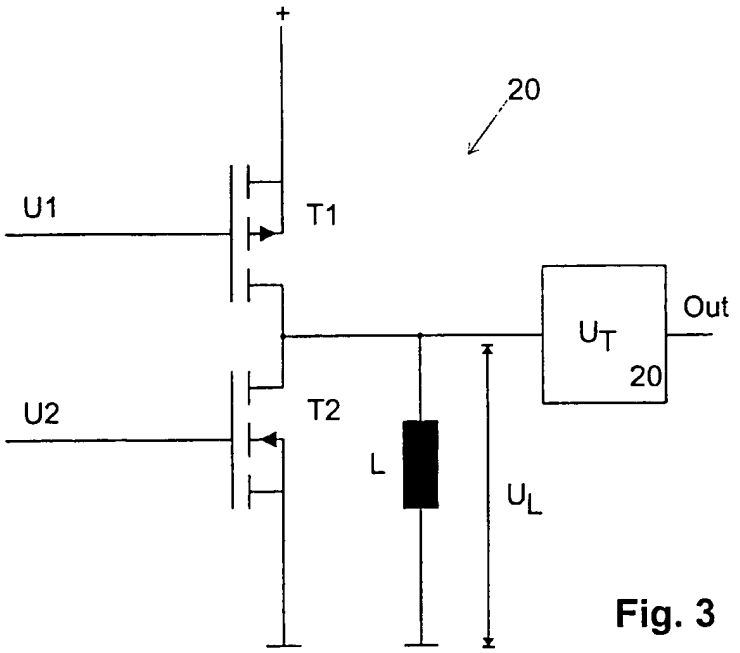

Fig. 3

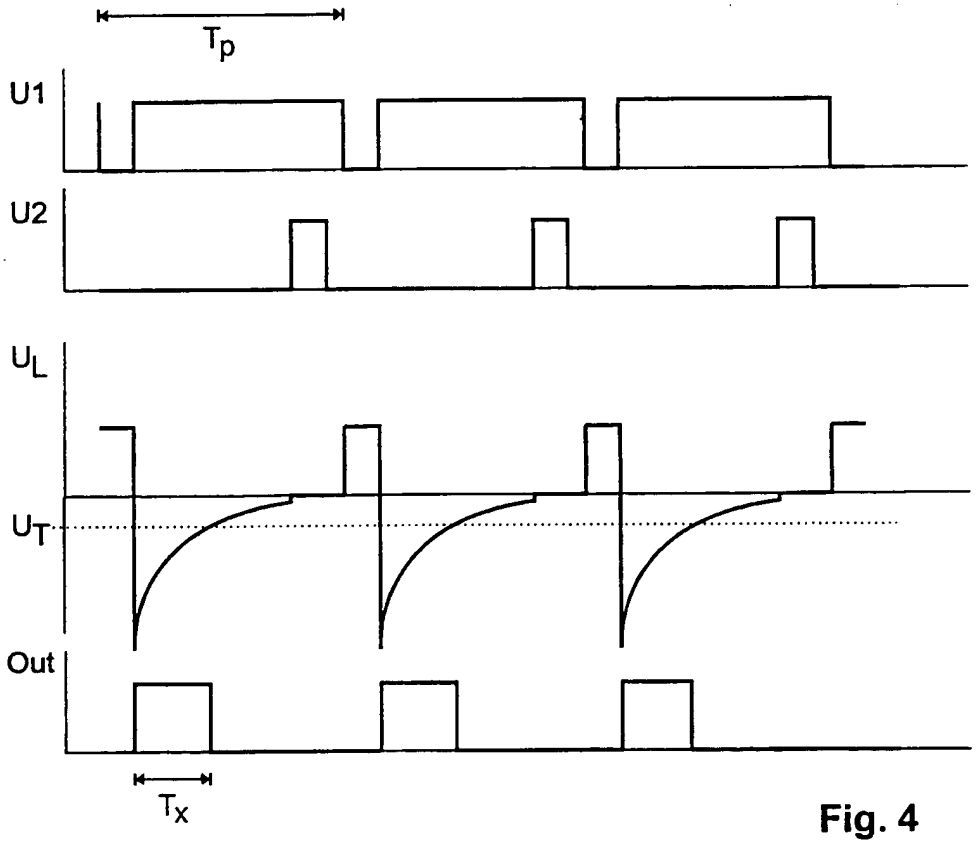

Fig. 4

measurement	measured value (mMol/L)	reference value (mMol/L)
1	4.80	4.871
2	5.30	5.290
3	6.00	6.132
4	20.90	21.144
5	16.80	16.940
6	5.40	5.510
7	6.30	6.447
8	7.75	7.844
9	4.90	4.809
10	4.60	4.561

Fig. 5

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/IB 00/01464

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00 A61B5/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 875 486 A (PANOSH RICHARD ET AL) 24 October 1989 (1989-10-24) column 4, line 47 - line 57 column 5, line 29 - line 42	1,2
A	column 7, line 19 - line 27	3,5-13
X	US 5 804 967 A (MILLER JOEL B ET AL) 8 September 1998 (1998-09-08) column 5, line 28 -column 6, line 52	5,9-13, 15
A	column 9, line 18 - line 29	1,3,4,14
A	WO 98 09566 A (INT DIAGNOSTICS TECHNOLOGIES I) 12 March 1998 (1998-03-12) page 25, line 13 - line 22 page 20, line 16 -page 21, line 3	1,3,5,6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2001	02/02/2001

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INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/IB 00/01464

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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information on patent family members

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